Practical Experience with Poliomyelitis Vaccine

Questions and Answers

Following the special session on Practical Experience with Poliomyelitis Vaccine at the 83rd Annual Meeting of the Association in Kansas City, Mo., the large audience supplied many questions, only a few of which could be answered at the time.

Knowing that these questions arose from genuine bafflement in the experience of many persons, it has been thought well to collect the entire list of questions and to have them answered by competent persons.

The Journal is indebted to Hart E. Van Riper, M.D., medical director of the National Foundation for Infantile Paralysis, Inc., New York, N. Y., for preparing the following answers. In several instances the names of experts chosen to answer questions have been appended to their replies.

It should be noted that these answers have been updated to February, 1956.

Historical Questions

1. *Was there on hand an adequate amount of vaccine to carry out the program of the National Foundation for Infantile Paralysis when results were given on April 12?*

2. *How long before there will be enough safe vaccine to take care of the 30–40 millions of dollars already appropriated for this purpose?*

3. *Do the experts really feel enough research had been done before undertaking the program launched after the report on April 12?*

1. In the light of what was then known about vaccine production, and if there had been no exceptional delays or difficulties, it is probable that there would have been enough vaccine available before the seasonable and regional advent of poliomyelitis to carry out the projected program of the National Foundation on schedule. This would have required about 18,000,000 cc of vaccine. There was not that much tested vaccine on hand on April 12, 1955.

2. This can only be guessed at—probably from 6 to 12 months.

3. Most experts in poliomyelitis were of the opinion that sufficient research had been done by April 12, 1955, to warrant a wide-scale vaccination program. If they had not been of this opinion, the 1954 field trial would not have been undertaken. A few experts disagreed with this opinion.

Is it true that a series of approximately six lots of vaccine were proved to contain live virus in Canada, about the month of May or June? This rumor is commonly heard.

In the first 21 vaccines prepared in the Connaught Medical Research Laboratories no lot was found unsatisfactory due to the presence of traces of living virus as demonstrated in tissue culture testing. Two lots of the 21 were not used because of possible lesions in the spinal cord of one monkey in the 36 used in testing each lot. Five additional lots of vaccine were prepared in April and May but were not distributed as traces of live virus were found in tissue culture testing in three of these in trivalent vaccine. Tests were not completed on one lot because of bacterial contamination.—R. D. Defries, M.D.

Have any members of the panel or resource persons had their own children or grandchildren given polio vaccine?

Yes. The children of Dr. Salk and Dr. Van Riper were among the very first to receive Salk vaccine.

Is there no competent, respected worker in virology or epidemiology who doubts (or has doubted) the effectiveness or safety (or both) of vaccine now being distributed?

There are doubtless some who have some reservations. The names of John Enders, Joseph Stokes, and Albert Sabin may be suggested.

Vaccine Field Trials

What percentage of children in the field trial were vaccinated and subsequently trans-

ferred to nonvaccinated group due to development of active disease within short period after vaccination?

Zero per cent. The children in the 1954 field trial who developed poliomyelitis within 30 days after vaccination were not transferred from one study group to another. They were eliminated from the statistical comparisons and calculations altogether.

Did you find clinical polio (paralytic or nonparalytic) in anybody with a titer of 1:4 prior to the diesase?

We have gone back to search the records of the Poliomyelitis Vaccine Evaluation Center very carefully in an effort to give an unequivocal reply and I have again reviewed the data on all cases of paralytic poliomyelitis. Consequently, I would submit the following reply:

Over 90 per cent of the patients with poliomyelitis had antibodies in their blood at the time the acute specimen was taken. These can be considered to have developed in the course of illness prior to that time.

Consequently, the only information to which one can refer the question is that obtained from children who were bled before vaccination or observation was begun. Unfortunately, only 24 cases were reported from this entire group.

There was one instance in an observed control child with a reported titer of 16 to Type 1 in blood taken June 23 whose onset was September 10, 1954. Type 1 virus was isolated from the stool. There was minimal paralysis recorded on the first examination. This appears to be the only case in which there is satisfactory evidence of antibody being present to an identified type of virus prior to onset.—Thomas Francis, Jr., M.D.

1. *Are we dealing with three vaccines: (1) 1954—Field Trials; (2) pre-May 27, 1955; and (3) post-May 27, 1955?*
2. *If so, has the most recent one had a field trial?*

1. No. There were no significant differences between the lots of vaccine used in the 1954 vaccine field trials and the vaccine used before and after May 27, 1955. There were differences in the details of the manufacturing process and the procedures of safety-testing for lots of vaccine produced and released in these three different periods, but the end-product, that is, the properly prepared Salk vaccine, was essentially the same.

2. The reported use of the vaccine in 1955, as presented to and by the Poliomyelitis Surveillance Unit of the U. S. Public Health Service, may be considered a field trial and a successful one.

Because of the study given to problems of manufacture and testing, it became possible in 1955 to produce effective vaccine more consistently than before. In this sense, that the chance of anything going wrong with the vaccine was reduced, the late 1955 product might be considered "superior" to the earlier lots.

Vaccine Safety and Safety Testing

What is the estimated calculated risk of inducing poliomyelitis infection by the inoculation of vaccine under present safety standards?

None. No risk.

Please explain the use of cortisone-treated monkeys in testing safety and what have been the results.

The administration of cortisone to test animals makes them more susceptible to poliomyelitis virus infection (and in fact to most other kinds of infection). Hence they are more sensitive to infection from vaccine samples should the sample contain live virus. However, the sensitivity of monkey tests used in testing the trivalent pools of Salk vaccine has also been greatly increased by simultaneous inoculation of the animals intramuscularly, intraspinally, and intracerebrally.

1. *Why is the vaccine tried on monkeys and not on other animals?*
2. *What type of monkey is used?*

1. Only the monkey is susceptible to poliomyelitis virus infection for practical testing procedures. (The cotton rat is also susceptible to Type 2 virus). However the virus pools are also tested on rabbits for the possible presence of B virus, on guinea pigs for *Mycobacterium tuberculosis* and on mice for lymphocytic choriomeningitis.

2. Cynomolgus and rhesus monkeys as a practical testing procedure.

What are the chances of activating a nonparalytic infection into a paralytic case by the present vaccine?

The chances are small. The expected good to be obtained outweighs the possibility of provocation. The risk is further reduced by performing inoculations in nonepidemic seasons.

What points can be presented to counter the assertion that the vaccine evaluated in 1955 produced its prophylactic effect because of the small amount of live polio virus present in the vaccine?

If there were live virus in the vaccine, it might be expected that a disproportionately large number of children and family contacts of children who received the vaccine would have shown evidence of some paralytic involvement, that is, clinically diagnosed poliomyelitis. This was actually the case *only* in the early instance where *known-faulty* batches of vaccine were used (chiefly in Idaho). There were no other epidemic circumstances in 1955 to suggest that live virus in the vaccine could possibly have been the cause. The Poliomyelitis Surveillance Unit of the U. S. Public Health Service noted on November 15, 1955, that among the nearly seven million children who received Salk vaccine in 1955 (except for the known-faulty lots), "no evidence has come to light that tends to incriminate any lot of vaccine of any manufacturer that has been released and used since the new safety standards were adopted."

The possibility that Salk vaccine prepared according to prescribed methods contains live virus which is responsible for antibody formation is altogether an hypothesis for which no proof has been presented. The present evidence of widespread use of the vaccine without infective consequences stands completely against this hypothesis.

Vaccine Manufacture

How long does it take to prepare each lot of vaccine if it passes each test satisfactorily? What is the shortest number of days?

A minimum of 120 days is required to complete the processing from virus culture to final testing of the packaged vaccine.

Do we know exactly what details of manufacture were at fault in the production of the batches of vaccine containing live virus and released last spring?

Unless we have this knowledge we cannot really safeguard against reoccurrence of this event except to hope that the more stringent sampling procedures will detect faulty batches.

This question cannot be answered directly in terms of the batches of vaccine containing live virus and released last spring. However, it can be said that the details of manufacturing, in respect to proper timing of the filtration steps in relation to the inactivation step, could have contributed to inconsistency in manufacturing. It has been reported that a rather high degree of inconsistency characterized the process applied by unnamed manufacturers.

It was realized, before last spring, and this has now been amply confirmed, that sampling procedures alone cannot be used to separate satisfactory from faulty batches of vaccine; therefore, one of the most important safeguards is the demonstration of consistency in the process as revealed by tests on consequent batches.

Thus, the safeguards against recurrence are not dependent upon more stringent sampling procedures, but upon the enforcement of the requirement for demonstration of consistency of manufacturing procedure as a prerequisite for the release of any one batch of vaccine; and upon the application of filtration and all other essential steps in a way that would achieve the desired degree of consistency. These are more fully discussed both in the Technical Committee's Report (J.A.M.A. December 10, 1955, p. 1444) and, also, in a paper in the January, 1956, issue of the American Journal of Public Health (Salk, Poliomyelitis Vaccine in the Fall of 1955).—Jonas E. Salk, M.D.

When and how was the problem of inadequate filtration of the vaccine, in commercial laboratories, first recognized?

The problem of inadequate filtration was recognized when samples of virus fluid, ready for the inactivation step, were carefully examined. It became clear that particles could readily interfere with complete inactivation. When adequate filtration was applied shortly before inactivation, rather than weeks or months previously, the irregularities that had heretofore been observed no longer occurred.—Jonas E. Salk, M.D.

Why is only formaldehyde and not other preservatives used?

Formaldehyde is not used as a preservative but as the inactivating agent. The formaldehyde is neutralized by sodium bisulphite before the final processing takes place.

Why use merthiolate?

Merthiolate is used as a preservative of the Salk vaccine—to suppress possible bacterial and fungal contamination. If the merthiolate is buffered with versene it does not reduce the potency of the vaccine upon storage. However merthiolate is only one of three preservatives now permitted in United States vaccine manufacture. (The other two are benze-

thonium chloride and methyl paraben and propyl paraben combined.) Vaccine manufactured in Canada does not carry a preservative.

Is preservative used at all in any of the vaccine? We had to use the entire 9 cc within six hours after the cap was pierced. Is this up to the particular drug companies?

A preservative is used in all vaccine produced and used in the United States at the present time. The purpose of the preservative is to protect against bacterial and fungal contamination. It is not necessary, therefore, to use the entire content of the vial immediately if it is properly refrigerated.

Epidemiological Questions

What about vaccinated children transmitting infections to parents and siblings?

Vaccinated children cannot transmit poliomyelitis infection to parents and siblings simply because they have been inoculated with properly prepared Salk vaccine, because there is no live virus in this vaccine to cause infection of the child into whom it is injected. If a child already has or later picks up a poliomyelitis infection *in spite of being vaccinated,* this infection could be transmitted to parents and siblings. The proved effectiveness of the Salk vaccine is to prevent paralytic involvement as a result of virus infection. It is not known to what extent it may suppress naturally acquired poliomyelitis infection of the nonparalytic type.

What is the significance in regard to a child who has been inoculated with live virus? Is such a child in any way a carrier and, if so, to what extent?

If a child became infected with poliomyelitis virus as the result of accidental inoculation with a live virus in an improperly prepared vaccine, he would be a carrier of the virus to the same extent as if he had a naturally acquired infection.

Even though the Salk vaccine has proved effective, have there been studies on the incidence in the parents of young children—roughly in the age group 25–34?

No studies specifically directed at this question have been reported; but much information has been gained as a by-product of other epidemiological and statistical studies of the incidence of poliomyelitis (paralytic and nonparalytic) in different age groups. These tend to show that there is an increase in the attack rate of paralytic poliomyelitis among parents of young children. The explanation of this phenomenon has not yet been fully made. It may be related to the number and ages of the children in the family, to the strain of pregnancy, to hygienic practices and standards within a household, or to other still undisclosed factors.

The 1954 Annual Statistical Review of the National Foundation for Infantile Paralysis showed that there was a slight increase in the number of reported hospital admissions for acute poliomyelitis among the 20–29-year-old age group as compared with 18- and 19-year-olds and with the 30 years and over groups. Age-specific case rates for poliomyelitis reported following the 1955 poliomyelitis epidemic in Massachusetts (New England Journal of Medicine, Jan. 19, 1955) reveal a slight upsurge in the 25–29 age group as compared with the five-year age groups immediately preceding and following. This was true both in 1955 and in the five-year average 1950–1954.

It is conceivably possible that the attack rate of poliomyelitis in parents of young children will be reduced by widespread vaccination of the children; but this is neither yet known nor proved. The difficult question of "herd immunity" is involved.

How many cases of paralytic poliomyelitis were prevented by the use of the Salk vaccine in the United States between April, 1955, and November 15, 1955?

Approximately 1,250 to 1,300 cases of paralytic poliomyelitis may be presumed to have been prevented in 1955 as a result of the use of the Salk vaccine. The statistical premises on which this estimate is based are as follows:

1. Seven million children (largely aged seven and eight) vaccinated at least once in 1955 NFIP vaccination program or 1954 field trials. Number vaccinated outside NFIP program unknown.
2. Twenty-eight thousand cases expected from end of May (when first inoculations were substantially under way) to December 31, 1955.
3. Fifteen thousand of these cases (54 per cent) could be expected to be paralytic on basis of experience in 1953 (53 per cent) and 1954 (56 per cent). This number is equivalent to a rate of 9.1 per 100,000.
4. Paralytic attack rate at ages seven and eight could be expected to be 24 per 100,000 (rate for all ages times 2.63), on basis of ratio of rate at ages seven and

eight to crude rates in 1952 (2.64), 1953 (2.83) and 1954 (2.41).

5. At rate of 24 per 100,000, one would expect 1,680 paralytic cases among 7,000,000 children aged seven and eight.
6. At 76 per cent effectiveness, as shown in Langmuir report to APHA, paralytic rate would be 5.76 per 100,000 and only 403 paralytic cases would occur, leaving difference of 1,277 paralytic cases prevented.

How many cases of paralytic poliomyelitis, primary and satellite, were induced by vaccine containing live virus since April, 1955?

The Public Health Service associated 158 cases with Cutter vaccine.

What is the correlation between the decision of Massachusetts to discontinue the program, their epidemic, and the fact that the company that supplied Massachusetts originally is no longer producing the vaccine? Why did Massachusetts stop?

The decision in Massachusetts to discontinue the state's vaccination program was not related to the onset of its polio epidemic. There was no suspicion that the vaccine was in any way responsible for the epidemic. The spread of the epidemic followed the classical radial pattern, spreading out from a hub in Boston. If the vaccine had been in any way involved, cases would have sprung up sporadically at the same time in different parts of the state.

The position of Massachusetts was stated in detail in a letter published in the December 1, 1955, issue of the New England Journal of Medicine and signed by 22 members of the Massachusetts State Polio Advisory Committee. This letter presents what the letter itself calls the committee's "conservative approach to the problem of mass inoculation with vaccine." The summary of the letter follows:

"The action of the Massachusetts State Polio Advisory Committee and the Massachusetts Department of Public Health was based on the following interpretation of the data available to them. The processing of the vaccine in large scale practice did not guarantee a non-infective product. Its release, therefore, was dependent upon clearance after negative results had been obtained in safety tests. There was reason to believe that the limit of sensitivity of safety tests designed to detect minute quantities of live virus had not yet been attained. Therefore, the possibility existed that live virus might, on rare occasions, escape detection in the vaccine. As long as any possibility remained that live virus of the Mahoney type might be present in any portion of the vaccine, it was considered that a risk to the individual and to the community still existed. The Committee gave special weight to the possibility that the establishment of the carrier state in inoculated individuals poses a hazard to the community."

In January, 1956, the Massachusetts State Polio Advisory Committee voted to resume vaccination with the present Salk vaccine in that state.

Vaccine Dosage Schedule and "Booster Shots"

What will be the recommended dosage schedule for 1956?

Two 1 cc injections, spaced from four to six weeks apart, intramuscularly or subcutaneously, with a booster injection at least seven months later.

How many and at what intervals are booster doses recommended for lasting immunity? After initial immunization, how often should "booster shots" be given to maintain adequate protection against paralytic disease?

After initial or primary immunization with two 1 cc injections spaced from four to six weeks apart, a first "booster" injection should be given at least seven months later. How frequently thereafter additional booster shots may have to be given to maintain adequate protection against paralytic disease is not yet known. This matter is the subject of continuing research on the part of Dr. Salk and others.

What is the maximum permissible interval between first and second doses of vaccine in the primary series? Will the second dose act as a "booster" if given from six to seven months after the first?

The first effective dose of vaccine is a sensitizing dose. The effect of such an injection is not lost if the second one is delayed for six months to a year, or even longer.

If the second injection is given six to 12 months after the first effective one, it will then act as a booster. However, if the second injection is given from four to six weeks after the first, the time will be too short between injections to obtain a true (very high titer of antibody) booster in the 80 per cent of children who were sensitized by the first injection. In the other 20 per cent the second injection acts as a primary sensitization.

It should be recognized that approximately 20 per cent of children injected with vaccine do not respond to the first injection with a measurable rise in antibody titer, such as occurs in the remaining 80 per cent. For this 20 per cent the second injection may be considered to be equivalent to the first effective injection.

Accordingly, the third dose, given six to 12 months after the two primary doses, is intended to act as the booster for all.

Do you feel that a second injection of vaccine at least seven months after the first would produce almost as satisfactory an antibody response as the three injections given in the recommended manner?

The answer to this question must be from the practical viewpoint rather than from the experimental or the theoretical. In selecting any *one* dosage schedule a number of factors must be balanced in trying to achieve a full effect in all persons inoculated. These factors are: (1) potency of the vaccine, (2) responsiveness of the individual, (3) the number, and (4) the spacing of the inoculations.

With vaccine of high potency, *two* injections, seven months apart, could be more effective than *three* injections of a vaccine of lower potency.

The dosage schedule presently proposed, involving three doses, is one that is designed for vaccines of the degree of potency now available and is easily and practicably achieved. One can accomplish the desired full effect more readily by multiple injections than by trying to increase vaccine potency beyond a reasonable point.

Nevertheless, a margin for effectiveness, to provide for contingencies of potency and individual responsiveness, must be considered; and it is for this reason that the recommended schedule was proposed.

Some children who have no antibody to any of the three types prior to inoculation do not develop antibody to all three types after the first dose, depending upon vaccine potency. If the second dose were not administered until seven months later, and such children did respond at that time, they can be said to have experienced primary immunization for the first time when given the second dose.

It is therefore proposed that for those who fail to respond the first time there is a second opportunity at the time of the second injection and, again, a third opportunity at the time of the third injection. In addition, there is then an equal opportunity for all to respond with the booster effect if, in fact, all have reacted by the time of the second dose whenever it was given, whether it be two weeks, four weeks, six weeks, or one year after the first.—Jonas E. Salk, M.D.

Why call the third dose a "booster" one, when it is really the completion of the vaccination?

On the same principle of antibody titer use then the second dose would also be a "booster."

This is partly a semantic question. It has become accepted usage to speak of the first two doses of Salk vaccine, spaced from four to six weeks apart, as the "primary immunization," the first effective dose being called a "sensitizing" dose.

It should be recognized that approximately 20 per cent of the children injected do not respond with a measurable rise in antibody titer to the first injection of Salk vaccine; for them the second injection appears to have the essential sensitizing effect.

When the third dose is given at least seven months later, the outcome of its effect is called "full immunization." The third dose is considered a booster because it ordinarily raises the level of antibody titer high above that attained with the first two doses.

There is a declining level of measurable antibody at the time that the third or booster dose raises it high above the levels obtained with the first two injections.

Will children have to receive a booster shot each year in order to insure protection?

Probably not; but how often remains to be determined by future observation and research. Dr. Salk has observed a comparatively high level of antibody persisting among children who received some of the first experimental injections of vaccine over two years ago.

Is there any possibility in the future just to give one inoculation of polio vaccine instead of three?

Not in the immediate future and not with the present Salk vaccine. While it is true that 1955 experience showed a surprising protective effect among children who received only one injection, the best present recommendation is to give two injections of 1 cc each, spaced from four to six weeks apart, with a third "booster" injection at least seven months later, for "full immunization."

Route of Vaccine Administration

What route of administration is recommended?

Intramuscular injection. With equal doses (1 cc) the evidence shows that intramuscular

injection effects a somewhat higher antibody response than subcutaneous injection. The volume of vaccine that can be effectively given by the intradermal route is limited, and the certainty is diminished of supplying an antigenic mass sufficient to achieve adequate antibody response.

Currently what method of administration (age group, size of dose, route—i.e. intramuscular vs. intracutaneous—number of doses) promises maximum possible decline in: (1) *polio incidence;* (2) *paralytic polio incidence for the coming summer months in view of probable level of supply?*

1. The effect of the vaccine on incidence of nonparalytic polio is unknown at the present time.

(2) The effectiveness of the vaccine in reducing the incidence of *paralytic* poliomyelitis in 1956, and presumably thereafter, will be in proportion to the number of children who actually are vaccinated. Based on 1954 (field trial) and 1955 experience, the incidence should be reduced at least 75 per cent among vaccinated children, possibly more. In the light of all factors of past experience with the vaccine and prediction of possible future supply, it is recommended that the dosage schedule remain what it was in 1955; namely,

Two 1 cc injections given from four to six weeks apart intramuscularly (or subcutaneously) with a "booster" injection of 1 cc at least seven months later.

The age groups eligible for vaccine are being determined by advisory committees of the several states. There are differences regionally in the peaks of incidence of poliomyelitis infection (with and without paralytic involvement). In general, children from one to 14 years and pregnant women are eligible for vaccine. However in some states the age limit has been raised to 19 years and dropped under one year. In other states a narrower age range, around the five to nine age group, has been established.

A Conference on the Use of Poliomyelitis Vaccine, convened in Washington, D. C., on Dec. 7, 1955, by the Surgeon-General of the U. S. Public Health Service, confirmed these recommendations.

What are Dr. Salk's ideas on the intradermal method of administration of the vaccine? Why not use it to make vaccine go farther?

While it is true that a significant antibody response can be elicited in a high proportion of individuals when 0.1 cc is given intradermally, it is equally true that a higher proportion respond when 1.0 cc is given intramuscularly or subcutaneously.

One can elicit antibody responses, over a wide range of dosage, whether vaccine be administered intradermally or intramuscularly or subcutaneously. One should refer not to the *intradermal method* versus some other method, but rather to a *smaller* versus the recommended larger dose.

The use of the intradermal route for administering vaccine provides an excuse for using less vaccine rather than that there is any sound immunologic reason for it. Since the objective is to produce the maximal practicable effect, the evidence suggests that this can be accomplished with greater certainty by using the larger volume.

The practical advantages of administration of vaccine intramuscularly or subcutaneously rather than intradermally is a further consideration beyond the greater assurance afforded by the larger volume to provide the extra margin toward the objective of full effectiveness for all.

The further advantage of the larger dose, either for primary or booster inoculation, is shown in the August 6 issue of the J.A.M.A., and in the January issue of the A.J.P.H., where it is made clear that greater amounts of antigen elicit a higher level of antibody.

This effect may be advantageous for providing the means for preventing not only paralysis, but infection as well and may thereby reduce the number of carriers. In this way the reservior may be reduced, thus protecting those who may not as yet have had an opportunity to receive vaccine. Thus, the more intensive immunization of the lower age group may affect the reservoir, and hence, the epidemic pattern, in a way that may, from the immediate as well as the longer term point of view, exceed the advantages of making vaccine go farther by using smaller doses. Any decision involves compromises so long as vaccine continues in short supply as related to the requirement for total immunization, whatever that requirement may be.—Jonas E. Salk, M.D.

Vaccine Supply and Priorities

How will vaccine be distributed to local health departments?

The distribution of Salk vaccine to local health departments will, in effect, be determined by state health departments and will, of course, depend upon available supplies of vaccine.

The details of this plan of distribution are spelled out in (1) a statement of Dr. Leonard

A. Scheele, Surgeon General of the Public Health Service, before the Senate Committee on Labor and Public Welfare on January 25, 1956; and (2) a Public Health Service Progress Report on the Poliomyelitis Vaccination Program as of January 24, 1956.

The parents of children in the first and second grades given the first and second shots want to know how and when the third or booster shot will come. What do we tell them?

When vaccine for the third or booster shot is available, it will be obtainable from local physicians or health departments. The situation will differ in different localities, for each state and county has the privilege of determining distribution of available supplies of vaccine within its own jurisdiction. This is a question that must be settled on the local community level. The situation as a whole is still fluid and overnight changes in recommendations and regulations may be expected, influenced by the local supply of and demand for vaccine. The National Foundation for Infantile Paralysis will not supply vaccine for the third or booster shot.

How can a medically indigent family actually get access to polio vaccine?

From a local physician or clinic established by local health authorities. This is entirely a local problem to be solved administratively in terms of customs, tradition, and practice in the community. The availability of vaccine will depend upon the state's supply of vaccine and the channels of distribution established by state, county, and local health authorities.

Has the National Foundation for Infantile Paralysis any plans for giving the third injection of vaccine?

None whatsoever.

Is the priority age now officially 0–15 and pregnant women?

Each state has the privilege of setting its own vaccine priority schedules. This is usually done by an advisory committee. In general the priorities have been set at from one to 14 years and pregnant women. In some states, however, the age range has been lifted and in others dropped.

Expiration Date and Storage of Vaccine

Do the present vaccines lose their potency with age? Do you recommend refrigeration storage of the vaccine?

The vaccine, under present standards, has a six months' expiration date. It should be stored under refrigeration at a temperature between 35° and 50° F, the lower limit being preferred. Freezing should be avoided.

How long can the vaccine be saved and used (refrigerated) after the vial is opened?

If a good technic is used in piercing the stopper of the vial, the remaining contents can be kept and used, if properly refrigerated, until the expiration date. It is not advisable actually to open the vial but simply to pierce the stopper with a needle.

1. *How long after expiration date is vaccine safe?*

Any polio vaccine released or cleared for use after May 27, 1955, the date of amendment of Minimum Requirements of the Public Health Service, is considered to be safe for use for an indefinite period of time after the expiration date. There is no evidence for diminishing safety of this product with storage.—David Bodian, M.D.

2. *How is the expiration date of a vaccine determined?*

According to requirements of the Public Health Service, the expiration date of polio vaccine is placed at six months after the date of manufacture or the date of issue. This dating is intended to safeguard potency of the product, since some preservatives, formerly in use, or poor condition of storage, are known to affect potency.—David Bodian, M.D.

3. *Must vaccine be immediately discarded on that date, or is there enough safety factor built in so that vaccine might still be used for another two weeks or even a month?*

With preservatives now in use, and with storage at ordinary refrigerator temperatures, it appears that the present dating of polio vaccine is conservative. It is almost certain that adequate potency is retained for at least several weeks after the expiration date, and probably much longer, under satisfactory conditions of storage.—David Bodian, M.D.

Clinical Questions

Should elective nose and throat operations be postponed until some recommended interval after the administration of vaccine?

Under ordinary circumstances, elective nose and throat operations are not performed during periods of high poliomyelitis incidence. If such an operation has to be performed during an epidemic period, it would be advisable to give two doses of vaccine and then wait a month, if such delay would not endanger the patient's life. Effective vaccination with a properly prepared and tested poliomyelitis vaccine greatly reduces the risk of paralytic poliomyelitis and does not engender or increase the chance of poliomyelitis infection. There is no reason, therefore, why elective nose and throat operations should be postponed following vaccination except that time be allowed for the protective effect of the vaccine to come into play.

What is the possibility of sensitization to penicillin and streptomycin from repeated injections of polio vaccine?

The fact is that such reactions have not been reported. Very small amounts of penicillin and streptomycin have been used in the vaccine. Siegal (The Penicillin Content of Poliomyelitis Vaccine (Salk) and Its Administration to Allergic Patients. A.J.P.H., June, 1955) reported that "the vaccine should offer no hazard either to persons allergic to penicillin or as a source of newly acquired penicillin sensitivity."

Miscellaneous Questions

The local health departments had voluntary help from the local physicians for the first two inoculations. Do you think the local doctors will give their time freely for the next program of inoculations from one to 14 and pregnant women, and if you do not think they will, how can the local health officer put across his program?

Some state and county medical societies have opposed the idea of doctors giving their services free for vaccine programs in 1956. The resolution of this question must be at the local level.

In the light of the proved effectiveness of the Salk vaccine, and the knowledge that its widespread use will prevent thousands of cases of paralytic poliomyelitis, it is hard to believe that local physicians will refuse to cooperate in developing and carrying out local programs of vaccination against paralytic poliomyelitis before the advent of the 1956 polio season. The magnitude of the problem of getting perhaps 35 million children inoculated (at least two injections) against paralytic poliomyelitis cannot be overlooked and perhaps should be stressed.

Physicians may properly look upon this problem as a *medical emergency* and not as a precedent for the future practice of medicine. Once the bulk of the child population is vaccinated against paralytic poliomyelitis, it may be expected that future vaccinations will be part of routine pediatric prophylactic procedure.

What is the difference between "accepted" and "reported" cases of poliomyelitis?

An explanatory note to Table 1 (Poliomyelitis Cases and Deaths Associated with Cutter Vaccine by State and Paralytic Status) of the paper, "The Surveillance of Poliomyelitis in the United States in 1955" by Alexander D. Langmuir, M.D., Neal Nathanson, M.D., and William Jackson Hall, Ph.D., presented before the American Public Health Association on November 15, 1955 (A.J.P.H. January, 1956), makes the following statements concerning "accepted" cases of poliomyelitis:

"Table 1 includes all cases associated with Cutter vaccine which have been 'accepted' by the Poliomyelitis Surveillance Unit through October 28, 1955. 'Accepted' cases meet the following criteria: (1) All cases have been classified as bona fide polio by the Polio Reporting Officer submitting the case; and (2) minimum essential data (county residence, age, sex, date of inoculation, date of onset, paralytic status and manufacturer of vaccine used) have been included in the report submitted.

"It should be noted that for the purposes of this presentation vaccine associated cases used in the tabulations were selected in the following way: (1) Vaccinated Cases: all cases included had onsets before June 1, 1955, so that no cases with onsets more than 50 days after inoculation are included; (2) Family Contact Cases: all cases included had onsets before June 15, 1955, so that no cases with onsets more than 65 days after inoculation of the vaccinated contact are included; and (3) Community Contact Cases: all accepted cases are included without restriction as to date of onset. However, reporting of Community Contact Cases was discontinued on August 1, 1955.

"These data are not final; minor additions, deletions, and corrections are to be expected."

Approximately how long will it be before a practical test is available to detect if a person has had polio—similar to the Schick test for diphtheria?

We have no easy, inexpensive test on the order of the Schick test for determining whether or not a person has had poliomyelitis. Several investigators are interested in and working on possible "skin tests" for the diagnosis and detection of poliomyelitis infection. How soon such tests will actually be developed to a point of practical usefulness, if they can be developed at all, is not known.

However there is available a time-consuming and rather expensive test for determining past poliomyelitis infection: the neutralization test, performed in tissue culture. This test takes about a week. Blood samples must be tested against all three types of polio virus separately.

The complement-fixation test is less expensive and less time-consuming but it has not yet been studied sufficiently to assure reasonably reliable findings.

To what extent is the polio vaccine being used in other countries of the world?

Why is Denmark interested in the vaccine research and not other European countries such as Western Germany and France?

Is the Soviet Union, including the satellites, using the vaccine?

The interest in the Salk vaccine, or modifications of it, is world-wide. Significant research has been conducted in many Western European countries as well as in Canada, where crucial steps in the development of large-scale vaccine production were taken.

Among the countries that have already reported to the World Health Organization on their vaccine research and vaccination plans and programs are the United States, Canada, Denmark, France, Germany, South Africa, and Sweden.

Great Britain has announced a vaccine program for 1956. Plans are also under way for such a program in Australia.

In January, 1956, four top-ranking Russian scientists, members of the Academy of Medicine of the U.S.S.R., visited the United States to get information about the Salk vaccine, presumably for introducing its use in Russia and satellite states. They were reported in the American press as saying that the development of the Salk vaccine showed "the great achievements of American science."

A meeting of experts from all parts of the world was convened by the World Health Organization in Stockholm, Sweden, on November 21, 1955. The following abstract from the report of this meeting reveals the extent to which many nations throughout the world were already working with the Salk polio vaccine in 1955:

Canada

Approximately 860,000 children between the ages of six and nine were injected with poliomyelitis vaccine manufactured at the Connaught Laboratories. Most received subcutaneous injections; about 100,000 intramuscular injections. The dosage was two injections of 1 cc each spaced four weeks apart. There was only one case in which there might possibly have been a relationship between vaccination and the occurrence of paralytic poliomyelitis.

Preliminary results up to the end of October were reported from four provinces. They indicated that among vaccinated children only 1.07 per 100,000 had contracted paralytic poliomyelitis, compared with 5.39 per 100,000 among the unvaccinated.

Denmark

In Denmark epidemics of poliomyelitis have presented a serious problem for many years. In 1952 for example, there were 2,450 paralytic cases in a population of 4½ million, a rate of 56.5 per 100,000 population.

As soon as the results of the 1954 vaccine field trials in the United States were announced, it was therefore decided to start poliomyelitis vaccination immediately. A vaccine was prepared at the Statens Serum-institut, closely following the methods described by Salk. However, the Type 1 strain used was Brunhilde.

An estimated 425,000 school children, approximately from seven to 12 years of age, which was about 98 per cent of the population at these ages, were given two simultaneous intradermal injections of 0.1 to 0.15 ml of the Danish vaccine, a total dose of 0.2 to 0.3 ml. The procedure was repeated after four to six weeks; and will be repeated again in nine to 12 months.

No cases of paralysis have occurred in any of the vaccinated children and no other serious reactions have been observed in the children.

An additional 250,000 children, aged nine months to seven years, were later vaccinated, also without serious reactions.

The protective value of the vaccine could not be fairly estimated in Denmark in 1955 because of the incidence of poliomyelitis in this year was so low. Only seven clinical cases were reported.

France

The Virus Division of the Institut Pasteur in Paris has since 1951 been selecting and studying strains of the different types of poliomyelitis virus with a view toward applying them to a vaccine. The production of an inactivated vaccine was considered mainly as an interim measure pending consideration of the use of a live attenuated vaccine in the future. An experimental group of children aged from two to seven years received three subcutaneous injections of an inactivated vaccine and have been followed for 14 months. No attempts at mass vaccination have yet been carried out in France. An extended field trial was planned but was postponed pending further information when news of accidents in the use of the vaccine in the United States was received in France.

Germany

In Germany the production of poliomyelitis vaccine on a large scale has been in progress at the Behringswerke since 1954. More than 1,500 liters of inactivated virus vaccine have been produced.

From November, 1954, to May, 1955, approximately 100,000 vaccinations were performed among children from one to 15 years of age. Most children received two intramuscular or subcutaneous doses of the vaccine. Exact figures are not known. However, no serious reactions have occurred and no case of paralytic poliomyelitis in a vaccinated child has been reported. In one instance a vaccinated child was thought to have died from poliomyelitis, but this could not be confirmed by laboratory tests.

South Africa

Since 1954 poliomyelitis vaccine has been produced in South Africa on a large scale in the laboratories of the Poliomyelitis Research Foundation. It has minor modifications from the methods used for producing the Salk vaccine in the United States. Trypsinized kidney cells of a South African vervet monkey were used to grow the virus. The Brunhilde strain for Type 1 virus was used and for Types 2 and 3 local South African strains (Collans and Templeon, respectively) were taken.

Following delays and doubts, prompted by reports from the United States, injection of approximately 15,000 children from ages six to 16 years, was finally undertaken in September, 1955. No case of paralytic poliomyelitis has been reported among the vaccinated children. There were two mild cases of skin rash, probably allergic.

Sweden

In Sweden a formalin-treated poliomyelitis vaccine, from virus grown on human embryonic tissue, has been produced and tested on a small scale. In February and March, 1955, a field trial of the vaccine in 2,000 school children was carried out—mainly to test antigenicity. The results were encouraging; no serious side-reactions of any kind were observed. However, on account of the reported vaccine accident in the United States and the failure of some Swedish batches to pass the safety tests, a scheduled vaccination program for the spring of 1956 was called off.

General Recommendations

1. The group [of WHO experts] considered that, subject to the application of the safeguards contained in [other] recommendations, the results obtained with poliomyelitis vaccine in mass immunization campaigns, already carried out in various countries, justified the conclusion that countries with a high incidence of paralytic poliomyelitis should plan to bring vaccination into routine use at an early date.

To put poliomyelitis control into proper proportion with other public health needs, such as rheumatic fever prophylaxis, how much—in percentages—would it be necessary to expand public health budgets, staff, and facilities?

It is impossible to answer this question. However, experience with poliomyelitis vaccination has shown a way toward expanded public health budgets, staff, and facilities. Expansion will occur to the extent that genuine public interest is elicited in the problems which public health can properly solve. There is no facile answer to the business of eliciting public interest and support for specific or general public health objectives. But it cannot be done with the left hand.

How much have the mistakes made in using this vaccine damaged experimentation among human beings with other health and medical programs in the future?

It is impossible to assess such a matter and it can be argued both ways. Mistakes may temporarily slow down progress but in the long run no permanent damage to progress results. The history of medicine is replete with events in which presumably helpful therapeutic and prophylactic agents have done harm. The famous "Lubeck incident" with

BCG vaccine, the introduction of faulty yellow fever vaccine in the 1940's and the still earlier experience with the original diphtheria toxin-antitoxin are well known examples of "mistakes" in the course of efforts to achieve valued prophylactic effects. Viewed in retrospect, these serious "mistakes" did not dangerously discourage progress toward the prevention of disease.

It may well be that the "mistakes" made in the course of using the Salk vaccine—mistakes that were all promptly recognized and corrected—will in the long run encourage experimentation among human subjects in other health and medical programs. The 1954 poliomyelitis vaccine field trial was, after all, the largest controlled clinical experiment in the history of medicine; and its purposes were enthusiastically supported both by the public and the professions.

The assumptions that "science is infallible" and that nothing new should be clinically tried before it is 100 per cent fool-proof are more damaging to scientific progress and human welfare than occasional, though tragic and regrettable, errors. Goethe's motto may be cited: "Mann irrt so lang er strebt" (Man errs so long as he strives).

We have not heard much about the National Foundation for Infantile Paralysis switching its field of interest to mental health since last April. Why?

In the immediate future the National Foundation for Infantile Paralysis has no intention of switching its basic field of interest. While the Salk vaccine is a magnificent weapon against paralytic polio, its mere existence is no guarantee that it will be used as rapidly and widely as it might be to reduce the threat of paralytic polio to the barest minimum.

Based on experience with the introduction of other prophylactic agents, it may be anticipated that years of earnest educational effort will be essential to obtain and retain maximum employment of vaccination for the prevention of paralytic polio.

The vaccine programs of 1954 and 1955 reduced the over-all incidence of paralytic poliomyelitis in the United States by something less than 10 per cent in 1955 (although the vaccine itself was at least 75 per cent effective in preventing paralytic polio among the age groups actually vaccinated). This means that there is still over 90 per cent of the way to go in actually eliminating paralytic poliomyelitis.

It should also be recognized that the National Foundation, and its 3,100 local chapters, have long-term commitments to aid financially those who were stricken with paralytic poliomyelitis in previous years and those who will become involved despite the Salk vaccine. It is estimated that there are perhaps 35,000 victims of paralytic polio in earlier years who can still benefit by the procedures and processes of total medical care and rehabilitation.

The extensive research and professional education programs supported by the March of Dimes have made impact in the total fields of virology and rehabilitation far beyond the prevention of paralytic polio and the treatment of polio patients.

Dental Officer Examinations

Applications are being accepted, until further notice, by the U. S. Civil Service Commission, for examination for dental officer in Grades GS-9 through GS-14. There is no written examination; applicants' qualifications are judged from a review of their experience, education, training, and on corroborative evidence obtained by the commission. There are openings in the field service of the Public Health Service throughout the country, and in departmental and field positions in various federal agencies in Washington and surrounding areas.

Applications should be sent to U. S. Civil Service Commission, Washington 25, D. C.